Prophylactic Use of Liposomal Amphotericin B in Preventing Fungal Infections Early After Liver Transplantation: A Retrospective, Single-Center Study

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ABSTRACT

In this study the authors evaluated the efficacy of prophylaxis with liposomal amphotericin B (L-AmB) in the incidence of fungal infections (FI) during the first 3 months after liver transplant (LT). The study was retrospective and accessed a 4-year period from 2008 to 2011. All patients who died in the first 48 hours after LT were excluded. Patients were divided by the risk groups for FI: Group 1, high-risk (at least 1 of the following conditions: urgent LT; serum creatinine >2 mg/dL; early acute kidney injury [AKI] after LT; retransplantation; surgical exploration early post-LT; transfused cellular blood components [>40 U]); and Group 2, low-risk patients. Group 1 patients were further separated into those who received antifungal prophylaxis with L-AmB and those who did not. Prophylaxis with L-AmB consisted of intravenous administration of L-AmB, 100 mg daily for 14 days. Four hundred ninety-two patients underwent LT; 31 died in the first 48 hours after LT. From the remaining 461 patients, 104 presented with high-risk factors for FI (Group 1); of these, 66 patients received antifungal prophylaxis and 38 did not. In this group 8 FI were observed, 5 in patients without antifungal prophylaxis ($P = .011$). Three more FI were identified in Group 2. By logistic regression analysis, the categorical variable high-risk group was independently related to the occurrence of invasive FI ($P = .006$). We conclude that prophylaxis with L-AmB after LT was effective in reducing the incidence of FI. No influence on mortality was detected.

FUNGAL INFECTIONS (FI) are infections caused by fungi and can occur in any part of the body. After liver transplantation (LT) and associated immunosuppression, FI, particularly systemic invasive FI (IFI), can occur more frequently and are regarded as the fourth most common type of infections in this patient group [1,2]. The incidence, although declining in recent years, may reach 40%, and most importantly, IFI carry a high mortality that is reported to be as high as 77% [3,4]. The most common pathogen is *Candida albicans*, followed by *Aspergillus* sp. These FI occur more frequently early after LT (up to 1 month), although 55% of *Aspergillus* sp infections occur in the first year after LT and 25% afterwards. Overall, FI due to *Candida* spp and *Aspergillus spp* account for nearly 80% of all FI in these patients.

It seems reasonable to prevent these infections using appropriate antifungal agents. Ideally, they should be able to treat the usual fungal pathogens in this group of patients, thus preventing all fungal infections, particularly IFI, and not interact with the common drugs used, as well as have an adequate safety profile. The most worrisome problems relate to initial liver function and avoiding further renal impairment.

Patient selection is another important issue. As the administration of prophylaxis to all patients undergoing LT is questionable, the most recent guidelines identify high-risk groups, in whom the incidence of FI and IFI is much higher [5]. Furthermore, the use of fluconazole is related to the emergence of mon-*Candida* spp, as well as

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fluconazole-resistant species [6]. Also, fluconazole is not active against *Aspergillus* spp.

The LT Center at Hospital Curry Cabral is the leading LT center in the country. The main specialty is the performance of sequential or domino LT, in which the liver explanted from patients suffering from familial amyloidotic polyneuropathy (FAP) are transplanted to recipients suffering from end-stage liver disease (ESLD). From 2007, liposomal amphotericin B (L-AmB) was proposed as a prophylactic agent in selected, high-risk LT patients. To test the efficacy of this prophylaxis, we performed a retrospective study on this issue, recovering the data for 4 consecutive years of LT and evaluating the incidence of IFI in high-risk patients, divided by those who received prophylactic L-AmB and those who did not.

MATERIAL AND METHODS

All patients who underwent LT from January 2008 to December 2011 were considered for enrollment. Patients who died intraoperatively and patients who died in the first 48 hours after LT were excluded. Patients were selected based on whether they were defined as high risk (Group 1) or low risk (Group 2). In Group 1, patients were further separated into those who received antifungal prophylaxis with L-AmB and those who did not. The incidence of FI was then evaluated and compared in all patient groups (Group 1 vs Group 2; and in Group 1, with and without prophylaxis). The prophylaxis with L-AmB was performed as intravenous administration of L-AmB, 100 mg daily for 14 days post LT. This administration started in 2007, but only became part of the protocol in 2012, so not all high-risk patients received it. All patients who undergo LT in our center also receive oral nystatin every 6 hours, and women receive vaginal clotrimazole once a day.

The high-risk group was defined by the presence of at least 1 of the following conditions: urgent LT due to acute liver failure or acute-on-chronic liver failure; serum creatinine >2 mg/dL previous to LT or hemodialysis previous to LT; early acute kidney injury (AKI) after LT with need for renal replacement technique; retransplantation; early post-LT need for surgical reintervention (mainly due to vascular complications and bleeding); transfused cellular blood components (red blood cell packed units [RBC] and platelet units >40 U) during LT.

Any fungal isolates were regarded as FI, whereas IFI was defined as proven or probable fungal infection in any body site or fluid obtained from a normally sterile site. Other isolates from non-sterile sites were considered non-invasive candidiases. [7,8].

The data collected for comparative purposes were the recipients' age and gender; surgery duration; duration of cold ischemia; pre-LT Model for End-stage Liver Disease (MELD) and Child-Turcotte-Pugh (CTP) scores; development of AKI after LT (using the AKI classification); hemodynamic instability during surgery (defined as the continuous infusion of vasopressor for more than 5 minutes); maximum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels after LT; number of RBC and fresh frozen plasma (FFP) units transfused during surgery; intensive care unit (ICU) and hospital stay; and type of LT (deceased-donor LT or sequential LT). The study period was extended for 3 months after transplantation. Occurrence of drug-related toxicity also was evaluated.

Deceased-donor liver grafts were harvested from brain-dead, heart-beating donors (the majority from other Portuguese institutions), preserved in Celsior solution and implanted in the recipient using the piggyback technique. In domino liver transplantation (DLT), the native hepatectomy in FAP patients, and the implantation of the deceased-donor graft also were done in standard piggyback fashion, with retrohepatic vena cava preservation and without venovenous bypass. FAP livers also were flushed with and preserved in the Celsior solution. As FAP liver grafts were harvested without the vena cava, the hepatic venous outflow of the domino grafts was reconstructed on the back table, using a vein graft from the deceased donor as previously described [9]. Following the reconstruction of hepatic venous outflow, the portal vein, hepatic artery, and bile duct were anastomosed.

The usual immunosuppressive therapy in use in our center consists of prednisolone, at a dose of 3 mg/kg i.v. in the first days, decreasing by 20 to 30 mg each day until reaching the maintenance dosage of 20 mg/day; mycophenolate mophetil 500 mg bid (according to platelet and white blood cell count); calcineirin inhibitors (CNI, cyclosporine A, 8 mg/kg/day; or tacrolimus, 0.1 mg/kg/day), to attain a target serum level of 350–400 ng/mL for cyclosporine A and 8–12 ng/mL for tacrolimus. Patients with renal impairment previous to LT received basiliximab 4 mg in the first day and 4 mg in the fourth postoperative day; in these patients, CNI is introduced after 7 days. All prescriptions are given by the hepatologist.

Before LT all patients must sign an informed consent document. Our protocol for data collection was reviewed and approved by the institutional ethic board.

Continuous variables are expressed as an average and standard deviation. Categorical variables are presented as categories with percentages. For comparative analysis, parametric (Student *t* test, for numeric variables, after confirmation of the normal distribution of data by the Kolmogorov-Smirnov test) and nonparametric tests (χ^2 test or Fisher's exact test, for categorical variables) were used. To establish dependence between variables, logistic regression analysis was performed (backward LR), using variables that were significant on univariate analysis, and a goodness-of-fit test (Hosmer-Lemeshow) was used to assess the fit of the logistic regression model. The dependent variable considered was the occurrence of FI when comparing patients in Group 1 who received prophylaxis with those who did not. A logistic regression analysis also was performed to establish the dependence of FI occurrence (FI as dependent variable) on the evaluated parameters. A P value <.05 was considered statistically significant. Statistical analysis was performed using SPSS 19.0 (Statistical Package for Social Sciences, SPSS Inc., Chicago, Ill., United States).

RESULTS

In the study period, 492 patients underwent LT. Of these, 31 died either during surgery or in the first 48 hours after LT and were excluded. Of the remaining 461 patients, 104 presented high-risk factors for FI (Group 1) and the other 357 did not (Group 2). Group 1 patients presented the following risk factors: acute liver failure or acute-on-chronic liver failure (23 patients); serum creatinine >2 mg/dL previous to LT or hemodialysis previous to LT (18 patients); early AKI after LT with need for renal replacement technique (7; with 17 patients developing AKI 3); retransplantation (16 patients); early post-LT need for surgical reintervention (mainly due to vascular complications and bleeding) (39 patients); and transfused cellular blood

components (red blood cell packed units [RBC] and platelet units >40 U) during LT (26 patients).

The characteristics of these groups are compared in Table 1. Group 1 patients had hemodynamic instability more often during surgery, as well as more severe AKI after LT; also, their MELD and CTP scores were higher. Duration of surgery was greater in group 1, although the duration of cold ischemia did not differ significantly.

In the high-risk group, 66 patients received antifungal prophylaxis and 38 did not. The comparative characteristics of these patients are presented in Table 2. The only difference between these groups is the number of required blood transfusions. Otherwise, they were similar in the studied parameters.

A total of 11 FI were identified (2.5% incidence in the cohort), 8 in the high-risk group (7% incidence). An FI was detected in 3/66 (4.5%) patients who received prophylaxis with L-AmB and in 5/38 (13.1%) patients who did not ($P = .011$). The FI detected were as follows: 2 biliary and 1 esophageal candidiasis in patients who received prophylaxis; and 3 esophageal, 1 candidemia, and 1 biliary in patients who did not receive prophylaxis. Seven isolates were *C. albicans*, and 1 was *Candida tropicalis* (a biliary candidiasis in a patient from the group that received prophylaxis). In low-risk patients 3 FI were observed: an esophageal and biliary, all *C. albicans*, and a *Candida parapsilosis* in the bloodstream. The average time from LT until the detection of IFI in the high-risk group was 27.8 days (minimum 6 days, maximum 81 days; with only 2 patients after 1 month).

After the 3-month period of the study and until the first year after LT another 9 FI were detected. Within the high-risk group, FI were detected in 4 patients of the group who received prophylaxis (3 oral candidiasis and 1 vaginal); and 1 oral candidiasis in the group who didn't receive prophylaxis. In the low-risk group from the 3rd to 12th month, 6 FI were observed: 2 urinary, 1 vaginal, and 3 oral candidiasis. In the low-risk group, 6 noninvasive fungal infections were observed: 2 urinary, 1 vaginal, and 3 oral candidiasis.

By logistic regression analysis, considering the entire cohort and IFI regarded as a dependent variable, only the variable high-risk group presented an independent relation to the occurrence of FI ($P = .006$, confidence interval 3.6–18.5).

In 1 patient, prophylaxis with L-AmB was discontinued due to a rise in serum creatinine levels.

DISCUSSION

The present study verified that antifungal prophylaxis with L-AmB was effective in reducing the incidence of FI in high-risk patients undergoing LT.

There are several descriptions of similar use of this drug in antifungal prophylaxis after LT in high-risk patients. However, the cohorts vary in dimension, time, and dosing regimens. Also, the majority of the available studies were published more than a decade ago. The study by Mora et al [10] used conventional amphotericin B in a dose of 1 mg/kg during 5 days; the study by Braun et al [11] used different doses of L-AmB, from 1 to 5 mg/kg until the discharge from the ICU); Lorf et al [12] used a dose of 5 mg/kg/day of L-AmB for 7 days; Castroagudin et al [13] used a dose of 1 mg/kg L-AmB for 7 to 10 days. Nonetheless, all these studies

Table 1. Patient Characteristics, Separated by Risk of Invasive Fungal Infection

	High-Risk Group (Group 1, n = 104)	Low-Risk Group (Group 2, n = 357)	*P* Value
Age (years, mean and SD)	47.8 ± 13.1	46.5 ± 12.7	ns
Male (n and %)	81 (77.9%)	246 (68.9%)	ns
Main pathologies (n and %)			
Acute liver failure	16 (15.3%)	0	
Compensated cirrhosis	65 (62.5%)	220 (65.2%)	
FAP	11 (10.5%)	104 (30.8%)	
Other	12 (11.5%)	13 (38.5%)	
Deceased-donor recipients (n and %)	95 (91.3%)	109 (30.5%)	<.001
MELD score (mean and SD)	15.6 ± 4.7	13.1 ± 3.8	.001
CTP score (mean and SD)	7.1 ± 2.4	6.1 ± 3.1	.028
Operative time (min, mean and SD)	344 ± 68.5	311.2 ± 55.1	.001
Cold ischemia time (min, mean and SD)	377 ± 66.3	368.9 ± 61.9	ns
Maximum ALT (IU, mean and SD)	2499 ± 3013	2152 ± 2658	ns
Maximum ALT (IU, mean and SD)	1451 ± 1316	1481 ± 1574	ns
Hemodynamic instability during surgery (n and %)	55 (52%)	65 (18.2%)	<.001
RBC (units, mean and SD)	7.6 ± 4.8	3 ± 3.1	<.001
FFP (units, mean and SD)	21.9 ± 12.9	9.2 ± 8.7	<.001
Mean AKI score (mean and SD)	1.3 ± 1.2	0.6 ± 0.9	<.001
ICU stay (days, mean and SD)	5.2 ± 3.1	2.1 ± 2.2	<.001
Hospital stay (days, mean and SD)	27.2 ± 11.2	17.1 ± 8.2	.001
Mortality (at 3 months)	13 (12.5%)	10 (2.9%)	<.001

Abbreviations: SD, standard deviation; FAP, familial amyloidotic polyneuropathy; MELD, Model for End-stage Liver Disease; CTP, Child-Turcotte-Pugh; ALY, alanine aminotransferase; AST, aspartate aminotransferase; IU, international units; RBC, red blood cell; FFP, fresh frozen plasma; AKI, acute kidney injury; ICU, intensive care unit.

Table 2. High-risk Patient Characteristics, Separated by Those Who Received Antifungal Prophylaxis and Those Who Did Not

	Received Antifungal Prophylaxis (n = 66)	Did Not Receive Antifungal Prophylaxis (n = 38)	*P* Value
Age (years, mean and SD)	48.4 ± 13.8	46.6 ± 11.7	ns
Male (n and %)	29 (64.4%)	21 (56.8%)	ns
Main pathologies (n and %)			
Acute liver failure or acute on chronic liver failure	12 (18.2%)	4 (10.5%)	
Retransplantation	12 (18.2%)	4 (10.5%)	
AKI or HD	17 (25.7%)	8 (21.0%)	
Other	25 (37.8%)	22 (58.0%)	
Deceased-donor recipients (n and %)	21 (56.8%)	23 (73.3%)	ns
MELD score (mean and SD)	16.1 ± 4.7	15.2 ± 4.4	ns
CTP score (mean and SD)	7.1 ± 2.3	7.2 ± 2.7	ns
Operative time (min, mean and SD)	348 ± 67.5	337 ± 72.8	ns
Cold ischemia time (min, mean and SD)	383 ± 73.4	362 ± 51	ns
Maximum ALT (IU, mean and SD)	2144 ± 1671	2958 ± 793	ns
Maximum ALT (IU, mean and SD)	1378 ± 1156	1577 ± 1544	ns
Hemodynamic instability during surgery (n and %)	44 (69.8%)	12 (52.2%)	ns
RBC (units, mean and SD)	8.2 ± 4.8	5.8 ± 4.4	.001
FFP (units, mean and SD)	23.7 ± 12.9	16.9 ± 11.7	ns
Mean AKI score (mean and SD)	1.2 ± 1.3	1.3 ± 1.1	ns
ICU stay (days, mean and SD)	5.4 ± 3	5.1 ± 3.4	ns
Hospital stay (days, mean and SD)	25.8 ± 11.4	27.4 ± 10.9	ns
Mortality	8 (12.1%)	5 (13.1%)	ns
Occurrence of IFI	3 (4.5%)	5 (13.1%)	.011

Abbreviations: SD, standard deviation; FAP, familial amyloidotic polyneuropathy; MELD, Model for End-stage Liver Disease; CTP, Child-Turcotte-Pugh; ALY, alanine aminotransferase; AST, aspartate aminotransferase; IU, international units; RBC, red blood cell; FFP, fresh frozen plasma; AKI, acute kidney injury; ICU, intensive care unit; IFI, invasive fungal infection; HD, hemodialysis.

concluded that this prophylaxis is effective in high-risk groups. In the present study we used a fixed dose of 100 mg/day L-AmB, roughly 1.5 mg/kg/day. At this dosage, it was observed by Singh and Paterson [14] that FI due to *Aspergillus fumigatus* can occur, thus suggesting higher doses for prophylaxis. No *Aspergillus* spp was identified during the study period. Moreover, only 2 systemic FI were detected, a lower than expected incidence. Other FI, namely oral, vaginal, and urinary, were not detected during the study period, although some occurred later. Perhaps, some role can be attributable to local antifungal prophylaxis with nystatin and clotrimazole.

Biancafiori et al [15] observed that not all patients undergoing LT benefit from antifungal prophylaxis using L-AmB as prophylactic drug. However, the definition of high-risk group, although important in patient selection, can also differ among studies. Despite these differences, the risk factors are now better characterized, and new scoring systems like MELD have entered clinical practice [16]. In our study we found differences between high- and low-risk groups in MELD and CTP score and operative time. Interestingly, cold ischemia time and data regarding early graft injury did not differ. Not surprisingly, the need for hemodynamic support and AKI development was higher in the high-risk group. In the low-risk group, more patients received grafts harvested from FAP patients. This data should be taken with caution. The high-risk group included patients with acute liver diseases, who underwent LT urgently. The FAP livers are preferentially allocated to patients with neoplastic diseases and stable liver cirrhosis. Nonetheless, these grafts are successfully transplanted with fewer postoperative complications, as described earlier [17].

We should note that the local conditions and specific agents may vary from center to center. In fact, during this extended period of observation, in our center only *Candida* spp was identified. Moreover, no *Candida glabrata* was isolated, thus characterizing the specific environment for fungal infections. This fact must be taken in consideration when analyzing the specific antifungal prophylaxis and treatment in different centers and countries. Taking this in consideration, the comparison between centers may be difficult.

The time for FI occurrence also agrees with that described in the literature [18]. Moreover, there was no death that could be attributable to FI, so this antifungal prophylaxis may contribute to the decrease in FI after LT, but not to mortality reduction, as sensed by several authors.

The overall incidence of FI was lower than described (2.5% in the entire cohort; 7% in the high-risk group). This fact may be related to the time period studied (2008 to 2011). Several conditions, such as improved surgical technique and better patient selection, are well described as influencing the incidence of fungal infections.

Several studies evaluated the use of amphotericin B lipid complex (ABLC) [19–22], using different doses (from 1 mg/kg/day to 5 mg/kg/day) and different times. In this study, the drug used was the liposomal formulation of AmB. We note that in some studies address ABLC and L-AmB as lipid formulations interchangeably and do not distinguish one from the other [23]. It may be useful to

recall some differences between them. The clinical use of this antifungal agent was precluded by their toxic effects [24]. One successful strategy used in the 1980s was the incorporation of these drugs in liposomes [25], lipid-based vesicles of concentric phospholipid bilayers separating water compartments. Several clinical studies have demonstrated that AmB was effective and less toxic than free AmB in the treatment of fungal infections. In 1995, after developing a new formulation of the previously described L-AmB, an amphotericin B lipid complex was described. It should be noted that all the lipid-based formulations of amphotericin B differ in their physicochemical properties in terms of size, lipid composition, shape, surface charge, drug-to-lipid ratio, and stability. With all these differences it is expected that their in vivo behavior will be different in terms of dosage, treatment schedule etc, as they are cleared differently and with different mechanisms from circulation [25–28]. Therefore, although the drug is the same, its pharmacology is different, and the appropriate dose must be carefully evaluated, defining a prophylaxis dosage and a therapeutic dosage. Nonetheless, all studies using lipid complex with amphotericin B also demonstrated to be efficacious in preventing IFI after LT.

Study Limitations

As pointed by some authors, the strength of a retrospective study is not comparable to that of a prospective, randomized, controlled study. The majority of the studies in this field are retrospective and use historical controls, so our study shares these deficiencies with most studies in the literature. The spectrum of antifungal therapy is now wide. No comparison between drugs was performed, although several other antifungal agents were successfully tested as prophylactic agents after LT.

The identification of FI is now supported by the use of molecular diagnosis, which we did not test. The use of this information may be included in future work.

CONCLUSION

Prophylaxis with L-AmB 100 mg daily for 14 days after LT was found to be effective in preventing IFI in high-risk patients after LT. The overall incidence of FI was 2.5% and 7% in the high-risk group. In this 4-year period, only *Candida* sp was detected, mainly *C. albicans*. No individual risk factor for IFI was superior. The accurate dose and prophylaxis time remain to be evaluated, considering local factors and most common isolates, which may vary from center to center.

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